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APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,493	07/18/2000	Jack Wands	MGH-0026	3498

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EXAMINER
SHUKLA, RAM R

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 03/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/600,493	Applicant(s) WANDS ET AL.
	Examiner Ram Shukla	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,6-8,11-28 and 32-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,6-8,11-28 and 32-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s) _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. The Examiner prosecuting this application has been changed. Any inquiries relating to the examination of the application should be directed to Examiner Shukla, whereas any inquiries relating to formal matters should be directed to Ms. Jacobs, Patent Analyst. The phone numbers for Examiner Shukla and Patent Analyst are provided at the end of this office action.

2. Applicants' amendment and response to the Office Action filed 1-8-02 have been received.

3. Claims 2 and 10 have been cancelled.

4. Claims 3, 4, 6, 11-13 and 32 have been amended.

5. New claims 34-46 have been entered.

6. Claims 3, 4, 6, 11-28, and 32-46 are under consideration.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 3, 4, and 6-8, 11-28, 32-46 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

Applicant is referred to utility guidelines published in Federal Register January 5, 2001, Volume 66, Number 5, Pages 1092-1099.

When determining whether an applicant has described the utility of invention, one has to determine whether the applicant has described a well-established utility. If not, has the application made any assertion of specific, substantial and credible utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for use. In contrast to general utility, a specific utility will be specific to the claimed subject matter. A substantial utility defines a real world

utility of the invention and utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context use are not substantial utility (see utility guidelines, in Federal Register January 5, 2001, Volume 66, Number 5, Pages 1092-1099).

It is noted that the claimed invention is directed to a recombinant nucleic acid molecule comprising a nucleotide sequence encoding hepatitis c virus NS3, NS4, or NS5 protein, operably linked to a promoter, enhancer, polyA, and 5' UTR of hepatitis C virus, a recombinant host cell comprising the nucleic acid molecule, a pharmaceutical composition comprising the nucleic acid molecule, and a method of inducing an immune response against hepatitis C virus in a human infected with hepatitis C virus by administering the pharmaceutical composition, and a method of treating a human infected with hepatitis C virus by administering the pharmaceutical composition.

First, it is determine whether the applicant has described the utility of invention. In the instant case the utility for the vector is for expression of the protein coding sequences comprised in the vector. Next the question is: is the utility credible and expression of a protein using an expression vector would be a credible utility. Next the question is: is the utility substantial and in the instant case the specification does not disclose a substantial utility. It is noted that the specification on page 2 lines 22-29 discloses that the HCV genome comprises 5' and 3' UTRs and that the 5' UTR is 324-341 nt long. The specification further discloses "This 5' UTR has been postulated to contain important regulatory elements for replication and/or translation of HCV RNAs". This indicates that the utility of the vector could not be substantial since its function is not known and therefore it's utility would require or constitute carrying out further research to confirm a real world use of an expression vector. It is emphasized that the specification as filed does not teach what would be a substantial utility of a nucleic acid molecule comprising a 5' UTR of HCV in addition to the components recited.

The instant invention is further not considered to have a specific and/or substantial utility because the specification fails to establish what is the function of the 5' UTR in context of expressing a protein from a nucleic acid molecule

comprising the nucleic acid molecule. Applicants have cited the references Han et al PNAS 1991 and Bukh et al PNAS, 1992, however none of these articles teach any regulatory property of the 5' UTR of HCV. In other words, the prior art does not teach the function of the HCV 5' UTR and therefore, the only immediate apparent utility for the instant invention would be its further scientific characterization as a putative regulatory sequence.

In view of the foregoing, one skilled in the art would not readily attribute any regulatory activity to the 5' UTR of HCV in context of a expression vector in view of the lack of any knowledge regarding the function of the 5' UTR in the prior art or in the specification. In view of such, it is unclear that a regulatory activity could be attributed to the 5' UTR in the claimed nucleic acid. Therefore, the asserted use for the claimed nucleic acid is not considered to support by either a specific and/or substantial utility, since no function can be ascribed to the gene.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 3, 4, and 6-8, 11-28, 32-46 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 3, 4, and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant nucleic acid molecule comprising a nucleotide sequence encoding hepatitis c virus NS3, NS4, or NS5 protein, operably linked to a promoter, enhancer, polyA, wherein the promoter is a CMV promoter and the enhancer is a Rouse sarcoma virus enhancer, a

recombinant host cell comprising the nucleic acid molecule does not reasonably provide enablement for a recombinant nucleic acid that comprises 5' UTR of hepatitis C virus in addition to the components listed above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

11. Claims 11-28, are 32-46 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 8-2-01 and as discussed below.

The invention as recited is drawn to a recombinant nucleic acid molecule comprising a nucleotide sequence encoding hepatitis c virus NS3, NS4, or NS5 protein, operably linked to a promoter, enhancer, polyA and optionally 5'UTR of hepatitis C virus. It is noted that while it was conventional in the art to make and use a nucleic acid molecule comprising a promoter, enhancer and polyA which are operably linked to a nucleotides sequence encoding a protein, such as hepatitis c virus NS proteins in the instant case, it was not conventional and routine in the art to use the 5' UTR of hepatitis C virus in an expression vector for regulating the expression of the nucleotide sequence encoding the protein. Han et al PNAS 1991 reported that the 5' UTR of hepatitis C virus has a very strongly conserved 5' untranslated region that is similar to that of pestiviruses in terms of its size, blocks, of homologous nucleotide sequences, and the organization of small open reading frames (ORFs) (see the last paragraph in the left column on page 1711). However, Han et al did not teach as to whether the 5' UTR increased or decreased expression of a coding sequence under its control. Likewise, Bukh et al PNAS, 1992, also characterized the 5' UTR of hepatitis C virus and noted that there is an important functional role of the 5' non coding region of the HCV genome (see the first paragraph in the left column on page 4942). However, these researchers did not teach if the 5' UTR of HCV regulated the expression of the gene under its control. In other words, the prior art does not teach the function of the HCV 5' UTR and

therefore, the prior did not teach how to use an expression vector that comprised the HCV UTR in the context of expressing a nucleotide sequence. The specification on page 2 lines 22-29 discloses that the HCV genome comprises 5' and 3' UTRs and that the 5' UTR is 324-341 nt long. The specification further discloses "This 5' UTR has been postulated to contain important regulatory elements for replication and/or translation of HCV RNAs". The specification also discloses the sequence for the 5' UTR of HCV on page 10 (lines 18-31 continued on page 11, lines 1-2), however the specification does not teach how to use the 5'UTR in the context of expressing the HCV nonstructural proteins and particularly when the nucleic acid containing the 5' UTR was to be used in treatment and in a pharmaceutical composition. It is noted that in a pharmaceutical composition or in a treatment method using a nucleic acid comprising a regulatory element, one would expect to get a higher gene expression due to the regulatory element. In the instant case, however, the specification does not does not teach how to use the 5' UTR of HCV for expressing a nucleotide sequence.

Next, the instantly presented claims recite "operably linked to a promoter, enhancer, polyadenylation sequence and optionally 5' UTR" however, the specification does not provide any guidance as to how could the 5' UTR be operably linked to the nucleotide sequence encoding HCV proteins. While it is known in the art how to operably link a promoter, an enhancer and a polyadenylation sequence, there is no teaching in the art to operably link 5' UTR to a nucleotide sequence encoding a protein and when a promoter, enhancer and polyA sequence are present in a construct. It is noted that the specification while disclosing the working examples did not use the 5' UTR sequences in making the vectors disclosed in the specification (see example 1). It is noted that while an artisan would know how to add the 5' UTR to a construct, the artisan would not know in what order or where in the vector in relation to other regulatory elements to put the 5' UTR. Furthermore, the specification does not teach how to use the claimed nucleic acid molecule for the intended use. An artisan therefore would have required extensive experimentation to make a nucleic acid molecule comprising a 5' UTR in addition to a promoter, an enhancer, a polyA sequence, and a nucleotide sequence encoding

the HCV NS proteins and use the nucleic acid molecule for the intended treatment method and compositions.

The pharmaceutical composition and the method of treatment stand rejected for reasons of record set forth in the previous office action of 8-2-01.

Response to Arguments

Applicants' arguments have been considered but are non-persuasive as discussed below. Applicants have reiterated their earlier argument that the claims do not recite a protective immune response and that they only recite inducing an immune response. Applicants have cited the case *Ex parte Erlich* in the support of their arguments. However, the cited case law is not applicable in the instant case since the issue is not a step of assay being not enabled, rather the issue is: is the invention enabled for the intended use as disclosed in the specification. As noted in the previous office action, the disclosure and claims clearly point out that the use of the claimed invention is for prophylactic or therapeutic use (see page 3 of the previous office action). As discussed in the previous office action, Examiner maintains the argument that there has been no demonstration of a prophylactic or therapeutic immunization based on the course of an HCV infection, but rather applicants conclusions are based on the effects of a mouse model in which the course of an HCV infection cannot be modeled. Accordingly, applicants arguments that mice are animal model for inducing immune responses in not relevant since it is not just inducing immune response but is their a therapeutic or prophylactic effect, particularly when mouse is not infected by HCV.

Applicants have argued that Houghton, Chattergoon and Encke et al do not support the position taken up by the office and that these references rather support the applicants' position. In response, it is reiterated that the review articles cited in the office action show the unpredictability of the state of the art and that the result obtained in mouse model is not predicative of and extrapolatable to human subjects. Furthermore, Houghton clearly lays out the fact that the development of an HCV vaccine is difficult and therefore, there would be further experimentation required

for developing a vaccine. Such experimentation would be undue because the model system used in the specification is not an art-recognized model for HCV infection in humans. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Furthermore, as set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictablility of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the invention as claimed.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2)

voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claims 3, 4, 6-8, 10-16, 45, and 46 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Jolly et al (US 6,297,048, 10-2-01, filing date 6-7-1995).

It is noted that this rejection is applicable to a composition of nucleic acid molecule that comprises a nucleotide sequence encoding HCV NS4 or NS5 proteins wherein the nucleotide sequence is operably linked to a promoter, an enhancer and a polyA sequence, a wherein the promoter is a CMV promoter and the enhancer is a RSV enhancer, and a host cell comprising the nucleic acid molecule.

Jolly et al teaches a recombinant retrovirus which expresses hepatitis c virus NS3/NS4, or NS5 antigen and host cells comprising the vector (see lines 48-59 in column 3, lines 1-12 in column 4, lines 56-67 in column 12, lines 20-38 and lines 49-67 in column continued in lines 1-21 in column 14, sections C and D in example 2, sections C and D in example 5, and examples 11 and 12) and a pharmaceutical composition comprising the nucleic acid molecule.

Regarding the limitation of bupivicaine, it is noted that it was conventional to use bupivicaine in a pharmaceutical composition, for example, see US 6,025,341, dated 2-15-00, claim 44.

14. No claim is allowed.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to **§** 1.121(c). For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Dianiece Jacobs whose telephone number is (703) 305-3388.

Ram R. Shukla, Ph.D.

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER